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Amendments to the Specification

Please replace the paragraph at page 1, line 6 with the following paragraph:

The present application is a continuation-in-part application of U.S. Patent Application No. 09/162,280, filed September 28, 1998, abandoned, which is a continuation-in-part application of U.S. Patent Application Serial No. 08/851,362, filed May 5, 1997, which issued as U.S. Patent No. 6,235,883.

Please replace the paragraph at page 8, line 21 with the following paragraph:

Figure 1 (SEQ ID NO: 29) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E1.1. Differences between the sequence encoded by heavy chain variable gene 4-31 and the sequence of the E1.1 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 8, line 27 with the following paragraph:

Figure 2 (SEQ ID NO: 3) is a nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 1 that was cloned out of the hybridoma E1.1.

Please replace the paragraph at page 8, line 29 with the following paragraph:

Figure 3 (SEQ ID NO: 40) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E1.1. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E1.1 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 9, line 4 with the following paragraph:

Figure 4 (SEQ ID NO: 4) is a nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule of Figure 3 that was cloned out of the hybridoma E1.1.

Please replace the paragraph at page 9, line 6 with the following paragraph:

Figure 5 (SEQ ID NO: 41) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E2.4. Differences between the sequence encoded by heavy chain variable gene 4-31 and the sequence of the E2.4 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 9, line 12
with the following paragraph:

Figure 6 (SEQ ID NO: 5) is a nucleotide sequence of
the cDNA encoding the heavy chain immunoglobulin molecule
of Figure 5 that was cloned out of the hybridoma E2.4.

Please replace the paragraph at page 9, line 14
with the following paragraph:

Figure 7 (SEQ ID NO: 42) is an amino acid sequence of
a kappa light chain immunoglobulin molecule that is secreted
by the hybridoma E2.4. Differences between the sequence
encoded by light chain variable gene 018 and the sequence of
the E2.4 secreted light chain are indicated in bold and
enlarged font. The contiguous sequence from CDR1 through
CDR3 is indicated by underlining and CDR1, CDR2, and CDR3
sequences are each indicated by double underlining.

Please replace the paragraph at page 9, line 20
with the following paragraph:

Figure 8 (SEQ ID NO: 6) is a nucleotide sequence of
the cDNA encoding the kappa light chain immunoglobulin
molecule of Figure 7 that was cloned out of the hybridoma
E2.4.

Please replace the paragraph at page 9, line 22 with the following paragraph:

Figure 9 (SEQ ID NO: 43) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E2.5. Differences between the sequence encoded by heavy chain variable gene 4-31 and the sequence of the E2.5 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 9, line 28 with the following paragraph:

Figure 10 (SEQ ID NO: 7) is a nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 9 that was cloned out of the hybridoma E2.5.

Please replace the paragraph at page 9, line 30 with the following paragraph:

Figure 11 (SEQ ID NO: 44) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E2.5. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E2.5 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through

CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 10, line 5 with the following paragraph:

Figure 12 (SEQ ID NO: 8) is a nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule of Figure 11 that was cloned out of the hybridoma E2.5.

Please replace the paragraph at page 10, line 7 with the following paragraph:

Figure 13 (SEQ ID NO: 45) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E6.2. Differences between the sequence encoded by heavy chain variable gene 4-31 and the sequence of the E6.2 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 10, line 13 with the following paragraph:

Figure 14 (SEQ ID NO: 9) is a nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 13 that was cloned out of the hybridoma E6.2.

Please replace the paragraph at page 10, line 15 with the following paragraph:

Figure 15 (SEQ ID NO: 46) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E6.2. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E6.2 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 10, line 21 with the following paragraph:

Figure 16 (SEQ ID NO: 10) is a nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule of Figure 15 that was cloned out of the hybridoma E6.2.

Please replace the paragraph at page 10, line 23 with the following paragraph:

Figure 17 (SEQ ID NO: 47) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E6.4. Differences between the sequence encoded by heavy chain variable gene 4-31 and the sequence of the E6.4 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 10, line 29 with the following paragraph:

Figure 18 (SEQ ID NO: 11) is a nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 17 that was cloned out of the hybridoma E6.2.

Please replace the paragraph at page 11, line 1 with the following paragraph:

Figure 19 (SEQ ID NO: 48) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E6.4. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E6.4 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 11, line 7
with the following paragraph:

Figure 20 (SEQ ID NO: 12) is a nucleotide sequence
of the cDNA encoding the kappa light chain immunoglobulin
molecule of Figure 19 that was cloned out of the
hybridoma E6.4.

Please replace the paragraph at page 11, line 9
with the following paragraph:

Figure 21 (SEQ ID NO: 49) is an amino acid sequence of
a heavy chain immunoglobulin molecule that is secreted by
the hybridoma E2.11. Differences between the sequence
encoded by heavy chain variable gene 4-61 and the sequence
of the E2.11 secreted heavy chain are indicated in bold and
enlarged font. The contiguous sequence from CDR1 through
CDR3 is indicated by underlining and CDR1, CDR2, and CDR3
sequences are each indicated by double underlining.

Please replace the paragraph at page 11, line 15
with the following paragraph:

Figure 22 (SEQ ID NO: 13) is a nucleotide sequence
of the cDNA encoding the heavy chain immunoglobulin
molecule of Figure 21 that was cloned out of the
hybridoma E2.11.

Please replace the paragraph at page 11, line 17
with the following paragraph:

Figure 23 (SEQ ID NO: 50) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E2.11. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E2.11 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 11, line 23 with the following paragraph:

Figure 24 (SEQ ID NO: 14) is a nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule of Figure 23 that was cloned out of the hybridoma E2.11.

Please replace the paragraph at page 11, line 25 with the following paragraph:

Figure 25 (SEQ ID NO: 51) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E6.3. Differences between the sequence encoded by heavy chain variable gene 4-61 and the sequence of the E6.3 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 12, line 1
with the following paragraph:

Figure 26 (SEQ ID NO: 15) is a nucleotide sequence
of the cDNA encoding the heavy chain immunoglobulin
molecule of Figure 25 that was cloned out of the
hybridoma E6.3.

Please replace the paragraph at page 12, line 3
with the following paragraph:

Figure 27 (SEQ ID NO: 52) is an amino acid sequence of
a kappa light chain immunoglobulin molecule that is secreted
by the hybridoma E6.3. Differences between the sequence
encoded by light chain variable gene 018 and the sequence of
the E6.3 secreted light chain are indicated in bold and
enlarged font. The contiguous sequence from CDR1 through
CDR3 is indicated by underlining and CDR1, CDR2, and CDR3
sequences are each indicated by double underlining.

Please replace the paragraph at page 12, line 9
with the following paragraph:

Figure 28 (SEQ ID NO: 16) is a nucleotide sequence
of the cDNA encoding the kappa light chain immunoglobulin
molecule of Figure 27 that was cloned out of the
hybridoma E6.3.

Please replace the paragraph at page 12, line 11 with the following paragraph:

Figure 29 (SEQ ID NO: 53) is an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E7.6.3. Differences between the sequence encoded by heavy chain variable gene 4-61 and the sequence of the E7.6.3 secreted heavy chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 12, line 17 with the following paragraph:

Figure 30 (SEQ ID NO: 17) is a nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 29 that was cloned out of the hybridoma E7.6.3.

Please replace the paragraph at page 12, line 19 with the following paragraph:

Figure 31 (SEQ ID NO: 54) is an amino acid sequence of a kappa light chain immunoglobulin molecule that is secreted by the hybridoma E7.6.3. Differences between the sequence encoded by light chain variable gene 018 and the sequence of the E7.6.3 secreted light chain are indicated in bold and enlarged font. The contiguous sequence from CDR1 through CDR3 is indicated by underlining and CDR1, CDR2, and CDR3 sequences are each indicated by double underlining.

Please replace the paragraph at page 12, line 25 with the following paragraph:

Figure 32 (SEQ ID NO: 18) is a nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule of Figure 31 that was cloned out of the hybridoma E7.6.3.

Please replace the paragraph at page 12, line 27 with the following paragraph:

Figure 33 provides a comparison of specific anti-EGF-r antibody heavy chain amino acid sequence comparisons (SEQ ID NOS: 42 to 49) with the amino acid sequence of the particular V_H gene which encodes the heavy chain of the particular antibody (SEQ ID NOS: 19, 22, and 40).

Please replace the paragraph at page 13, line 1 with the following paragraph:

Figure 34 provides a comparison of specific anti-EGF-r antibody light chain amino acid sequence comparisons (SEQ ID NOS: 24, 26, 28, 34, 30, 36, 32, and 38) with the amino acid sequence of the particular V_K gene which encodes the light chain of the particular antibody (SEQ ID NOS: 20 and 41).

Please replace the paragraph at page 14, line 3 with the following paragraph:

Figure 39 shows that human anti-EGF-r antibodies derived from XenoMouse II strains inhibit growth of SW948 cells *in vitro*, where ~~(⊖)~~(●) depicts the results achieved by an anti-EGF-r antibody in accordance with the invention, (□) depicts the results achieved by the murine monoclonal antibody 225, and (▲) depicts the results achieved by a control, nonspecific, human IgG2 antibody.

Please replace the paragraph at page 14, line 22 with the following paragraph:

Figure 43 shows data related to the eradication of an established human epidermoid tumor in nude mice through use of human anti-EGF-r antibodies in accordance with the invention *in vivo*. In the Figure, ~~(▲)~~ (Δ) depicts the results achieved with multiple doses of 1 mg each of a human anti-EGF-r antibody in accordance with the present invention (E7.6.3), (X) depicts the results achieved with two doses of 125 μg each of doxorubicin, (*) depicts the results achieved with a multiple doses of 1 mg each of a human anti-EGF-r antibody in accordance with the present invention (E7.6.3) in combination with two doses of 125 μg each of doxorubicin, (■) depicts the results achieved by a control, nonspecific, human IgG2 antibody, and (◆) depicts the results achieved utilizing phosphate buffered saline as a control.

Please replace the paragraph at page 15, line 1 with the following paragraph:

Figure 44 shows data related to the eradication of an established human epidermoid tumor in nude mice through use of human anti-EGF-r antibodies in accordance with the invention *in vivo*. In the Figure, (◆) depicts the results achieved with multiple doses of 0.5 mg each of a human anti-EGF-r antibody in accordance with the present invention (E2.5), (■) depicts the results achieved with two doses of 125 µg each of doxorubicin, (▲) (Δ) depicts the results achieved with multiple doses of 0.5 mg each of a human anti-EGF-r antibody in accordance with the present invention (E2.5) in combination with two doses of 125 µg each of doxorubicin, (X) depicts the results achieved utilizing phosphate buffered saline as a control, and (*) depicts the results achieved utilizing a control, nonspecific, human IgG2 antibody at a dose of 1 mg.

Please replace the paragraph at page 16, line 3 with the following paragraph:

Figure 48 shows the inhibition of *in vitro* tumor cell proliferation by anti-EGFr antibodies. A431 (A) or MDA-468 (B) cells were cultured with anti-EGFr MAbs (E7.6.3; ◆ 225; ▲ 528) or control human myeloma IgG₂K (O), as described in Materials and Methods. Cell viability was assayed by crystal violet staining. Data presented as % of cell growth inhibition.

Please replace the paragraph at page 16, line 8 with the following paragraph:

Figure 49 shows the eradication of established A431 tumor xenografts by E7.6.3 MAb. A431 cells (5×10^6) were injected s.c. into the nude mice on day 0. A. At day 7 when tumor size reached an average volume of $0.1 \sim 0.25 \text{ cm}^2$, mice ($n = 5$) were injected i.p. with PBS (O) or with 1 mg of either E7.6.3 (◆) or the control human myeloma IgG_{2k} (■) antibodies twice a week for three weeks. B. when the mean tumor sizes reached 0.13 (▲), 0.56 (▼), 0.73 (◆) or 1.2 (●) cm^3 , mice ($n=10$) were treated with 1 mg E7.6.3, twice a week for three weeks. Control mice (O, $n=10$) received no treatment. C, at day 10 when tumor sizes reached 0.15 cm^3 , mice ($n = 8$) were injected i.p. with $200 \mu\text{g}$ (∇) or $50 \mu\text{g}$ (Δ) doses of E7.6.3, or $200 \mu\text{g}$ (▼) or $50 \mu\text{g}$ (●) doses of 225 MAbs, twice a week for three weeks. Control mice (O) received no treatment. Tumors were measured weekly and their volume was measured as described in "Materials and Methods". The data is presented as the mean tumor size \pm SEM.

Please replace the paragraph at page 17, line 23 with the following paragraph:

Figure 57 (SEQ ID NO: 55) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.1 hybridoma.

Please replace the paragraph at page 17, line 25 with the following paragraph:

Figure 58 (SEQ ID NO: 56) provides oligonucleotide and amino acid sequence information on the light chain of the antibody produced by the E20.1 hybridoma.

Please replace the paragraph at page 17, line 27 with the following paragraph:

Figure 59 (SEQ ID NO: 57) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.3 hybridoma.

Please replace the paragraph at page 17, line 29 with the following paragraph:

Figure 60 (SEQ ID NO: 58) provides oligonucleotide and amino acid sequence information on the light chain of the antibody produced by the E20.3 hybridoma.

Please replace the paragraph at page 18, line 1 with the following paragraph:

Figure 61 (SEQ ID NO: 59) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.8.1 hybridoma.

Please replace the paragraph at page 18, line 3 with the following paragraph:

Figure 62 (SEQ ID NO: 60) provides oligonucleotide and amino acid sequence information on the light chain of the antibody produced by the E20.8.1 hybridoma.

Please replace the paragraph at page 18, line 5
with the following paragraph:

Figure 63 (SEQ ID NO: 61) provides oligonucleotide
and amino acid sequence information on the heavy chain of
the antibody produced by the E20.11.2 hybridoma.

Please replace the paragraph at page 18, line 7
with the following paragraph:

Figure 64 (SEQ ID NO: 62) provides oligonucleotide
and amino acid sequence information on the light chain of
the antibody produced by the E20.11.2 hybridoma.

Please replace the paragraph at page 18, line 9
with the following paragraph:

Figure 65 (SEQ ID NO: 63) provides oligonucleotide
and amino acid sequence information on the heavy chain of
the antibody produced by the E20.18 hybridoma.

Please replace the paragraph at page 18, line 11
with the following paragraph:

Figure 66 (SEQ ID NO: 64) provides oligonucleotide
and amino acid sequence information on the light chain of
the antibody produced by the E20.18 hybridoma.

Please replace the paragraph at page 18, line 13
with the following paragraph:

Figure 67 (SEQ ID NO: 65) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.19.2 hybridoma.

Please replace the paragraph at page 18, line 15 with the following paragraph:

Figure 68 (SEQ ID NO: 66) provides oligonucleotide and amino acid sequence information on the light chain of the antibody produced by the E20.19.2 hybridoma.

Please replace the paragraph at page 18, line 17 with the following paragraph:

Figure 69 (SEQ ID NO: 67) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.21 hybridoma.

Please replace the paragraph at page 18, line 19 with the following paragraph:

Figure 70 (SEQ ID NO: 68) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E20.22 hybridoma.

Please replace the paragraph at page 18, line 21 with the following paragraph:

Figure 71 provides a mutation analysis of antibodies in accordance with the invention (SEQ ID NOS: 39, 41, 43, 45, 47, 49, 75, 51 and 53). In particular, the sequence

of the E20.21 antibody, which comprises a VH 4-31 heavy chain is shown.

Please replace the paragraph at page 18, line 24 with the following paragraph:

Figure 72 (SEQ ID NO: 69) provides oligonucleotide and amino acid sequence information on the heavy chain of the antibody produced by the E7.5.2 hybridoma.

Please replace the paragraph at page 18, line 26 with the following paragraph:

Figure 73 (SEQ ID NO: 70) provides oligonucleotide and amino acid sequence information on the light chain of the antibody produced by the E7.5.2 hybridoma.

Please replace the paragraph at page 48, line 15 with the following paragraph:

Poly(A)⁺ mRNA was isolated from approximately 2×10^5 hybridoma cells derived from immunized XenoMice using a Fast-Track kit (Invitrogen). The generation of random primed cDNA was followed by PCR. Human V_H or human V_κ family specific variable region primers (Marks et. al., 1991) or a universal human V_H primer, MG-30 (CAGGTGCAGCTGGAGCAGTCIGG) (SEQ ID NO: 1) was used in conjunction with primers specific for the human Cγ2 constant region (MG-40d; 5'-GCTGAGGGAGTAGAGTCCTGAGGA-3') (SEQ ID NO:2) or Cκ constant region (hκP2; as previously described in Green et al., 1994). Sequences of human

Application No. 09/187,693
Response dated October 3, 2003
In Response to August 27, 2002 final Office Action

Mabs-derived heavy and kappa chain transcripts from hybridomas were obtained by direct sequencing of PCR products generated from poly(A⁺) RNA using the primers described above. PCR products were also cloned into pCRII using a TA cloning kit (Invitrogen) and both strands were sequenced using Prism dye-terminator sequencing kits and an ABI 377 sequencing machine. All sequences were analyzed by alignments to the "V BASE sequence directory" (Tomlinson et al., MRC Centre for Protein Engineering, Cambridge, UK) using MacVector and Geneworks software programs.